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ROLE OF NANOTECHNOLOGY IN ORAL CANCER DIAGNOSIS AND THERAPEUTICS

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Oral cancer is a multifactorial disease, but tobacco is considered as the most predominant attribute for its advancement. It can be preventable by the interruption of risk factors. Its early detection can minimize its detrimental effects and can improve the quality of life as well as morbidity and mortality of the patients. Nanotechnology is a very different field that has transformed the industry and is setting new directions in the treatment of oral cancer. Nanotechnology conversed methods can be used in cancer treatment. They can aid to have a better diagnosis with limited injurious substance. Nanotechnology is a very different field that has revolutionized the industry and is setting current directions in the management of oral cancer. The application of Nanotechnology significantly benefits clinical practice in diagnosis, treatment, and management of cancer. Hence, Nanotechnology can be also accustomed to molecular imaging accompanied by tomography and photoacoustic imaging of tumors and management of cancer as photothermal and radiotherapy. Nanotechnology a succeeding generation techniques have numerous advantages to treat patients of cancer from diagnosis to treatment.

INTRODUCTION

Cancer is a major cause of death, the second most common cause in the world, exceeded only by heart disease and is a compound group of diseases with numerous possible causes. The causes of cancer involve genetic factors; lifestyle factors such as the use of tobacco, diet, and physical activity; certain types of infections; and environmental exposures to other types of chemicals and radiation. Oral cancer (OC) is one of the most common cancers in the world, four-fifths of what manifested in developing countries. [1] It is estimated that the number of current cases of all cancers global will be 12.3 and 15.4 million in the year 2010 and 2020, respectively.

Numerous risk factors or possible causative agents for OC have been described. Chemical factors like tobacco and alcohol, biological factors like human papillomavirus (HPV), syphilis, oro-dental factors, dietary deficiencies, chronic candidiasis, and viruses have been shown to be crucially related to oral cancer.[2]

The most prevalent oral cancer treatments are restricted to chemotherapy, radiation, and surgery. Limitations in the treatment of oral cancer are a consequence of new challenges seen in cancer therapies today, involving lack of early disease detection, non-specific systemic distribution, insufficient drug concentrations reaching the tumor and incapacity to monitor therapeutic responses. The poor delivery system of drug and residence at the target site leads to significant complications, such as multi-drug resistance.[3]

Recent clinical diagnostic techniques typically involve an invasive biopsy. Further histopathological diagnosis is based on morphological and structural changes at the cellular or tissue level, which may not be obvious for early stage tumors. [3]

Nanotechnology has the capability to offer solutions to these common obstacles in cancer therapies, due to its characteristic size (1-100 nm) and large surface-volume ratios.[4] It was first suggested by the Nobel Prize winner Richard Feynman in 1959. Nanotechnologies may have properties of self-assembly, stability, specificity; drug encapsulation and biocompatibility as a result of their material composition.[5] Nanoparticles illustrate unique size-dependent physical and chemical properties, which can be optical, magnetic, catalytic, thermodynamic, and electrochemical. These particles have great potential for clinical use, and the National Institute of Health (Bethesda, MD, USA) has referred to this area as Nanomedicine. Thus, nanotechnology can help in the early detection of tumors and oral cancer therapeutics. The well-studied nanoparticles include quantum dots (QDs), carbon nanotubes, paramagnetic Nanoparticles, liposome, Gold Nanoparticles and many others.[6]

Application of nanotechnology is revolutionizing biomedical engineering by allowing latest types of drug delivery, production of tissue modules, the advancement of biomaterial and improved surfaces for medical devices, in vitro in vivo methodologies, biofiltration systems, and robotic assembly, among many other exciting advances. Studying dental structures and surfaces from a nanoscale perspective leads to a better understanding of the structure-function physiological relationship of dental surfaces. In selective, diseases such as tooth hypersensitivity, dental caries and oral cancer can be quantified based on morphological, biophysical and biochemical nanoscale properties of tooth surface itself and dental materials or oral fluids such as saliva. Nanotechnology offers a broad range of innovations and improvement in prevention, diagnostics, and treatment of oral diseases.[7]

PHYSIOLOGY OF NANOPARTICLES

Nanoparticles exist in the same size as proteins or cells; it is suitable for tagging or labeling which function efficiently in a living organism whose cells are generally 10 μm across. However, the cell parts are much less and are in the sub-micron size domain. Even smaller are the proteins with an average size of just 5 nm, which is approximate with the measurement of smallest manmade Nanoparticles. This simple size resemblance gives a suggestion of applying Nanoparticles as very fewer probes that would permit us to spy at the cellular machinery besides establishing too much of the interference. A compact control of the typical size of particle size and a narrow allocation of sizes allow generating very potent fluorescent probes that emit narrow light in a very broad range of wavelengths. This aids in producing biomarkers with numerous and well-illustrious colors. The size of Nanoparticles in the range of 200 nm is known to accumulate at the solid tumor site by the improved permeation and retention effect. Plasmonic NPs conjugated to nuclear targeting peptides cause damage of DNA and apoptotic populations in cancer cells. These NPs specifically target tumor cells, resulting in minimal damage to healthy tissues.[3]

ADVANTAGES OF NANOPARTICLES

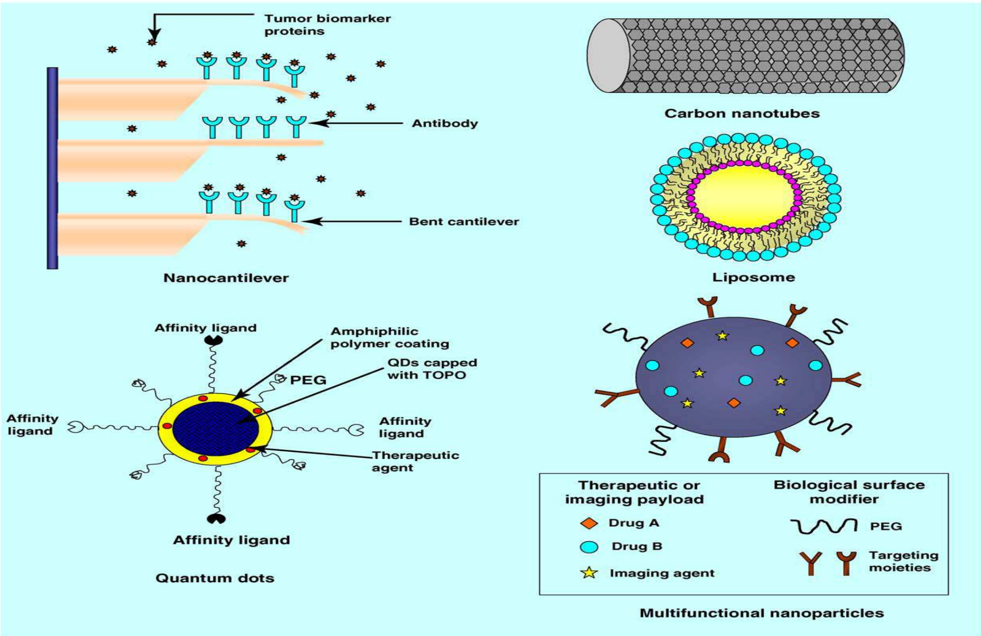
The employ of Nanoparticles has not only revolutionized the field of medicine but has helped in accurate, precise management of diseases, drug delivery. Various other uses of Nanoparticles in various fields of medicine and cancer are fluorescent biological labels, drug and gene delivery, bio-detection of pathogens, tumor destruction through heating (hyperthermia), detection of proteins, probing of DNA structure, tissue engineering, separation and purification of biological molecules and cells, phagokinetic studies and MR imaging contrast enhancement.[3] [Table 1].

Table 1: Advantages and disadvantages of Nanoparticles [3]

Types	**Advantages**	**Disadvin1ages**
Gold nanoparticles	Increased contrast Less invasive No photobleaching	Biocompatibility Optical signal not strong Toxicity Tumor targeting efficacy of low
Quantum dots	Multiple Molecular Targets simultaneously Fluorescence of high quality and energy	Toxicity effect of metal Core
Nanocapsules	Efficient drug accumulation at the site Sustained drug release for weeks	
Carbon nanotubes		
Liposomes	Less cytotoxic Biocompatibility Biocompatibility Isolation of drug from Surrounding environment Ability to entrap both hydrophilic And hydrophobic drugs	

NANOMATERIALS

Nanomaterials in one dimension are termed as sheets, in two dimensions as nanowires, nanotubes and as quantum dots in three dimensions. Their properties contrast from other materials due to two reasons; the increase in surface area and quantum effects. Nanomaterials due to their small size have a much-increased surface area per unit mass compared to bigger particles. All properties, including electrical, optical and magnetic ones, are altered. Nanotechnology has applications in many fields such as medicine and dentistry.[8]



Various tools of nanotechnology for cancer therapy. A liposome is composed of lipid structures that can be manufactured stealth by PEGylation and enveloping diverse therapeutic agents; these are used as a conceivable Nanocarrier for cancer therapy. Nan cantilevers are array-like construction in which engineered small bars attached at one end assist in the recognition of changed proteins present in certain types of cancers. Through the time of the procedure of detection, on one side the cantilever bends, which is observed optically. Quantum dots are fluorescent Nanocrystals that can be combined to ligands by enclosing a polymeric layer onto it; therapeutic agents are enveloped and used for the treatment of cancer. Current synthetic techniques have been advanced to design multifaceted Nanoparticles, in which we can enclose both imaging agents and therapeutic in a one Nanocarrier system that will combine with more than one ligands on the surface; thus, it will act as a novel multifunctional Nanocarrier system with the capacity of targeted tumor imaging and the delivery of therapeutic agents.[9]

NANOTECHNOLOGY IN DIAGNOSIS OF ORAL CANCER

It can be described as the application of nanotechnology for clinical diagnostic purposes advanced to appropriate the needs for raised sensitivity and earlier detection of disease. Nanotechnology has restructured the detection and treatment of cancer. It has the potential to identify even a particular cancerous cell in vivo and transport the highly toxic drugs directly to the cancerous cells. Nanoshells, quantum dots, carbon nanotubes, and currently synthesized nanosponges are few of the materials used for the detection of cancer.

Applying particular cross linkers like specific antibodies against cancer cells, individual cancer cells can be detected. A novel set of lipid-coated; directed quantum dots could be used for quantifying numerous specific biomarkers on the exteriors of individual cells of cancer.

- ❖ Nanoscale cantilevers: Elastic beams used to attach with cancer linked molecules
- ❖ Quantum dots: These glow very brightly in ultraviolet light. They attach to proteins associated with cancer cells, thus localizing tumors
- ❖ Nanotubes: Carbon rods that can detect affected genes and also localize their location
- ❖ Nanopores: Small holes that enable DNA passage one strand at a time, thus making DNA sequencing highly efficient
- ❖ Cantilever array sensors: Ultrasensitive mass detection technology

- Nanoelectromechanical Systems: Convert biochemical to an electric signal
- Multiplexing modality: Sensing large numbers of different biomolecules simultaneously.[10,11]

NANOMATERIALS FOR ORAL CANCER DIAGNOSIS

The Early revelation of cancer will greatly raise survival rates. An in situ tumor will be simple to eliminate than one that has metastasized. Various types of NPs are satisfactory for gene and drug delivery, probing DNA structures, etc., they involve:

- Liposomes
- Solid lipid particles
- Inorganic NPs (e.g. Gold and Magnetic Nanoparticles)
- Nanocrystals
- Polymer Therapeutics such as dendrimers, fullerenes.
- Polymeric NPs (Nanosphere and Nanocapsules)

Kah et al. in their study demonstrated the capability of antibody conjugated gold NPs to target and under a reflectance-based optical imaging system, they emphasize the cancer cell. In certain, they have demonstrated that gold NPs can supply an optical contrast to discriminate among normal and cancerous cells and their combination with antibodies also permits them to map the expression of significant biomarkers for molecular imaging.[12]

NANOTECHNOLOGY IN TREATMENT OF ORAL CANCER

- Nanovectors for gene therapy
- Nonviral gene delivery systems
- Nanomaterials for brachytherapy: BrachySilTM
- Drug delivery across the blood-brain barrier.[9, 11]

Nanotechnology is possibly the single method that can be used for site-specific action without producing side effects by destructing the normal cells. Cancer nanotechnology is the current trend in the treatment of cancer. It shows a great expectation for enhancing cancer therapies by acting at least at two main levels: conferring current properties to a pharmaceutical agent (modified pharmacokinetics, increased stability and decreased toxicity, etc.,) and targeting the agent straightly to the tumor.[13] A policy could be to relate antitumor drugs with colloidal NPs, with the aim to overcome the cellular and noncellular based system of resistance and to enhance the selectiveness of drugs direct cancer cells while decreasing their toxicity toward normal tissues. NPs can deliver drug delivery carriers of transporting chemotherapeutic agents or curative genes into malignant cells while preserving healthy cells. This may permit for minor doses of toxic substances as the drugs are targeted directly to the target tissue.[14] Few nanoscale delivery devices, like dendrimers, ceramic NPs, silica coated micelles, and cross-linked liposome can be delivered to cells of cancer. This advances the selectivity of drugs toward cancer cells and will decrease the toxicity to normal tissue. This is done by attaching monoclonal antibodies or cell surface receptor ligands that bind particularly to the cells of cancer. Surface modification of NPs can also increase the permeability of drugs and gives an option to generate high permeability NP⍰based cancer therapeutics. Research on the covalent attachment of peptidic membrane translocation sequences has helped this concept. With improved cell permeability, NPs can become more therapeutically effective drug transport vehicles.[15] NPs have a size of 5 nm to 200 nm, allowing their unique interaction with biological systems at the molecular level. As a result of their composition, NPs are capable of self-assembly and maintaining stability and specificity which are crucial to drug encapsulation and biocompatibility.[16] Combinational chemotherapy combined with nanomedicine has unclosed a current horizon to the new therapeutic approaches that have collapsed due to tumor cell resistance and undesired toxicity to normal cells. Although, aggressive advances could be manufactured when nano-based drug delivery systems coupled with combination chemotherapeutic agents. Doxorubicin encapsulated or combined with divergent Nanocarrier to increase it's particularly on targeting the cancerous cells. DOX nanocarrier complex adhered to specific antibodies such as epidermal growth factor receptor or folate receptors which are profusely demonstrated on the surface of cancerous cells. Both oral and intravenous formulation of doxorubicin is accessible. Apoptotic effects on cancer cells were revealed succeeding topical administration of 5fluorouracil matrix tablets on a three spatial outgrowth model of oral squamous cell carcinoma (OSCC); demonstrating that locoregional chemotherapy of OSCC could be successful. It has been effectively shown that modified chitosan NPs loaded with 5aminolevulinic acid were taken up by cells of oral cancer through folate receptor intermediate endocytosis.[17,18,19,20]

NANOTECHNOLOGY-BASED DRUG DELIVERY SYSTEMS

On the basis of nanotechnology, Nanocarrier manufactured from organic and inorganic materials have been advanced, like liposome, micelles, hydrogel, liquid crystals etc.[6] They have shown high potential in the treatment of cancer by increasing the accomplishment of medicines. Recent PNPs were fabricated from biocompatible/ biodegradable polymers, like polyethylene glycol (PEG), poly (γ-benzyl glutamate), poly-D, L-lactide, polylactic acid, poly D, L-glycolide, polylactide, co-glycolide, gelatin, sodium alginate, polycyanoacrylate and chitosan, polysaccharides and proteins. They presented physical stability, controlled release and excellent tolerability protection of incorporated labile drugs from degradation, thus, they can be used for various routes of administration, like oral, ocular, dermal, pulmonary and rectal.[12]

LIPOSOMES

A liposome is a small bubble/vesicle, made out of the identical material as a cell membrane. It can be filled with drugs and used to deliver drugs for cancer and other diseases. Liposomes have been effectively examined for the transport of chemotherapeutic drugs to improve the efficacy of remedial treatment and reduce the toxicity to normal cells. Synthetic cationic liposomal DNA called lipoplexes, Liposome-based for gene therapy, have clear potential, especially for oral cancer treatment. Nanocarrier encounters various shields en route to their target areas, such as mucosal barriers and non-specific uptake.

MICELLES

Micelles are colloidal dispersions manufactured from amphiphilic molecules which tend to be ~20-80 nm in breadth. Their minor size, when compared to great Nanocarrier such as a liposome, can restrict their capability to transfer a substantial dose of the chemotherapeutic agent to the tumor. In supplement, currently, hyaluronic acid (HA)-paclitaxel combine micelles have been presented to be far additional cytotoxic in the direction of HA receptor over showing cancer cells than for HA receptor defective cells.

HYDROGEL

It is a network of hydrophilic polymeric chains distributed in water that could swell and deliver drugs for decomposition and disintegration between the spaces in their mesh. They are attractive for oral application because their polymeric chains can approximately communicate with saliva glycoprotein, generating a mucoadhesion phenomenon. Application of hydrogel as chemotherapeutic drug delivery systems for drugs including paclitaxel, doxorubicin, DTX, tamoxifen, and cisplatin. It is described that the SAHA cisplatin/ PECE hydrogel system with direct intratumoral injections may be a functional procedure for the treatment of oral cancer and other solid tumors. In universal, conventional chemotherapeutics drugs exhibit poor systemic stability, limited water solubility, unwanted drug-related side effects (bone marrow depression and nephrotoxicity) and a relatively short half-life that prevent their further clinical application.

Cis-Diamine-dichloro platinum (cisplatin, CDDP) is one of drug which is considerably used for the treatment of many cancers such as testicular, ovarian and oral squamous cancers, however, it suffers from various significant side effects. Studies have shown that Nanocarrier caused better selective accumulation of CDDP in tumors while lessening its distribution in normal tissue. Therefore, biodegradable polymer, poly (lactic-co-glycolic acid) PEG (PLGA-PEG) based self-assembled polymeric micelles were designed in a study conducted by Wang et al. The hydrophilic poly (ethylene glycol) shell layer enables the particles to circulate for a long time in the blood compartment which will facilitate its preferential accumulation in the tumor tissues.[12]

CURRENT ADVANCES

At present, the majority of commercial Nanoparticles applications in medicine are geared towards drug delivery. In biosciences, Nanoparticles are replacing organic dyes in the applications that necessitate high photo-stability as well as elevated multiplexing capabilities. The chief trend in supplemental development of nanomaterials is to make them multifunctional and controllable by exterior signals or by the local environment thus fundamentally turning them into nano-devices.

CANCER NANOVACCINES

The earliest type, prophylactic vaccines, triggers humoral and cellular immunity and is administered into healthy individuals in order to avoid them from getting cancer. The human papillomavirus vaccine is an example of a prophylactic vaccine. For those who already have cancer, there is a second type of vaccine called cancer Nanovaccine. They could be designed, manufactured and introduced into the human body to improve health, including cellular repairs at the molecular level. The Nanovaccine is so small that it can easily enter the cell; therefore, Nanovaccine can be used in vivo or in vitro for biological applications. This has lead to the advancement of contrast agents, diagnostic devices, analytical tools, application of physical therapy and drug delivery vehicles. The consumption of drug and related side-effects can be considerably lowered by depositing the active agent at the preferred location.

NANOMEDICINE HEAT THERAPY

Similar to radiotherapy for cancer, heat therapy uses Nanoparticles and hence that management is targeted at the cancer cells. Resembling radiation therapy, a laser optic probe is used, which principally ensures that the infrared radiation is directed at the tumor and allows the management to be through the skin, from outside the body. Therefore, this new heat treatment is very similar to the current method of radiation therapy, but the Nanoparticles alter the treatment in that they cause minimal damage to the healthy tissue.[3]

CONCLUSION

Nanotechnology has the capability to enhance both the diagnosis and treatment of this disease. Conjugating Nanoparticles with current advances in diagnosis, in supplementary to the biological and chemical therapies has enormous scope and potential. Nanotechnology has earlier shown to be potent in transporting anticancer drugs, improving the adequacy and decreasing side effects. So, it's a boon in oral cancer diagnosis, therapeutics, and prevention of cancer disease. It will transform dentistry, healthcare and human life more profoundly than many other developments of the past. In the coming years, it will play a key role in early disease detection, diagnostic and therapeutic procedures to improve oral health and general well⍰being of humankind.

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